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Alleviating Skin Picking Behavior in Prader-Willi Syndrome Using Selective Serotonin Reuptake Inhibitors and Topiramate: A Review of the Literature

This paper discusses what is known currently about treating skin picking behavior in people with Prader-Willi Syndrome using Selective Serotonin Reuptake Inhibitors and topiramate. Because of small samples and flawed methodology it is argued that the advantages and disadvantages of either drug therapy are not fully known at this time, but that future research is strongly indicated. Some suggestions for further studies are discussed.

The importance of establishing an effective treatment of the self-injurious behavior of skin picking in those with Prader-Willi Syndrome is well documented. Warnock and Kestenbaum (1992) reported that skin picking is frequent within the population and often results in continuous lesions that can necessitate stays in a hospital for treatment. Skin picking can bring about sepsis, acute hemorrhaging and deep wounds (Hellings & Warnock, 1994). Benjamin and Buot-Smith (1993) recorded a case of skin picking, of a 9-year-old boy that tore at "scabs through muscle down to bone and ate his flesh" (p. 870). Another case report reviews a woman with a history of hospitalization for treating sepsis in self-inflicted wounds who stated that the behavior was something that made her happier (Warnock & Kestenbaum, 1992). Skin picking is one of a variety of behaviors seen in

Prader-Willi Syndrome that families have a hard time managing (Smathers, Wilson, & Nigro, 2003). It can be seen then, that attenuating skin picking is not only important for the medical health of persons with Prader-Willi Syndrome, but also for their psychological health and that of their families.

Prader-Willi Syndrome Defined

Prader-Willi Syndrome (PWS) is a genetic disorder caused by a mutation on chromosome 15q11-q13 by a lack of expression of the father's genes or by uniparental disomy in which two copies of the maternal chromosome are seen. It is manifested in an average of 1 in 10,000 births. The major diagnostic criteria of PWS includes: hypotonia and feeding complications in infancy, obesity, short stature, hypogonadism, mild to moderate mental retardation, and hyperphagia.

Beyond physical ailments, there are many characteristic behavioral problems associated with PWS. Some include: temper tantrums, violent outbursts, obsessive-compulsive behavior, stubbornness, argumentativeness, lying, stealing, and skin picking.

Skin Picking

Wigren and Heimann (2001) reported skin picking to be widespread within a sample of 37 people with PWS. Parents reported that two-thirds, or 65%, of their children with PWS exhibited the behavior. The action was seen among all ages and both sexes, showing that it is not limited to a specific developmental period or gender within the population.

Although Wigren and Heimann's (2001) study is limited by its methodology, as the researchers did not directly observe behavior but instead employed parental questionnaires and follow-up phone calls, many important aspects of skin picking were documented. Data collected suggested that skin picking behavior begins early in life, with an average of 73% of the participants having started before the age of seven. The researchers saw a stable rate of incidence of the behavior over the life spans of people with PWS. This may allow for prognosis of life long severity of skin picking by the age of seven. We should be aware, however, that this data could be faulty because of the possibility of recall bias of the parents answering the questionnaires.

Another important finding was that the rate of skin picking had a high positive correlation with the rate of occurrence of temper tantrums and overall spontaneous aggression, as well as the self-injurious behaviors of hair and clothes pulling (Wigren & Heimann, 2001). These findings may help caretakers and physicians to anticipate coping strategies as well as treatments for the symptom cluster.

Research concerning the extent of skin picking and correlated behaviors in PWS is minimal. Based on these preliminary findings, however, it seems logical to suggest that further research is needed to obtain a clearer clinical

picture of how skin picking may inform other behavioral issues in PWS.

Treatment

Selective Serotonin Reuptake Inhibitors (SSRIs), and topiramate have both been used in attempting to alleviate skin picking in persons with PWS. SSRIs are a class of drug often used in treating depression, anxiety, and personality disorders. Hellings and Warnock (1994) speculate that skin picking may be caused by a reduced amount of serotonin in the central nervous system. They explain that SSRIs increase the level of serotonin in the body by reducing its ability to be taken up from the synaptic cleft in neurons. Several studies (Dech & Budow, 1991; Hellings & Warnock, 1994; Warnock & Kestenbaum, 1992) that employed the use of SSRIs indicate that they have been successful in treating the symptoms of self-injurious behavior, including hair pulling and skin picking, in people with Obsessive Compulsive Disorder.

Topiramate has been a more recently investigated drug in treating skin picking. It is an anticonvulsant used for treating epilepsy. Privitera (1997) describes a number of different theories to explain how topiramate reduces seizures, but the mechanism remains uncertain. Through a review of the literature, Privitera proposes that, when at the right dosage, topiramate might "act through...sodium channels, γ -aminobutyric acid (GABA), and a specific subtype of glutamate receptor" (p. 1165) by inhibiting neurons that trigger seizures. The forerunners of topiramate research in skin picking in PWS (Shapira, Lessig, Murphy, Driscoll, & Goodman, 2002) began testing the drug partly because of Privitera's (1997) assertion that it does not have the side effect of weight gain that is common in other anticonvulsants. This is a significant issue as most patients with PWS die because of complications of obesity (Dech & Budow, 1991).

A survey of 369 caretakers of people with PWS taken in 1994 discloses that both SSRI's and anticonvulsants have the same rate of

response in treating skin picking (Stein, Keating, Zar, & Hollander, 1994).

SSRI Research

While experimenting with SSRIs was popular in the 1990s, relevant research has since dropped off with no clear conclusions as to their benefits in treating skin picking in PWS. In four small studies with one to four patients each (Benjamin & Buot-Smith, 1993; Hellings & Warnock, 1994; Warnock & Kestenbaum, 1992; Yaryura-Tobias, Grunes, Bayles, & Neziroglu, 1998) that incorporated the SSRI fluoxetine, also known as Prozac, and in one case study using the SSRI fluvoxamine (Martin et al., 1998), skin picking was said to improve markedly. Three of these studies (Benjamin & Buot-Smith, 1993; Hellings & Warnock, 1994; Warnock & Kestenbaum, 1992) quantified improvement by observation of lesions and reported that not only did existing sores heal, but also no new ones were found over the course of treatment. However, none measured this in a systematic way, such as photographing and documenting the size of sores weekly, but instead relied on varied periodic visual checks. Systematic check-ups must be done carefully, however, as they could be detrimental to treatment because of the possibility that skin picking could be exacerbated by intensified observation (Hellings & Warnock, 1994).

Although Yaryura-Tobias et al.'s (1998) publication claims a favorable outcome in skin picking with the use of fluoxetine over a four-year period, there are several reasons to question those findings. First, there is no mention of measurements gathered by the research team. They did monthly check-ups in a clinical setting, but did not report what was done during these evaluations. Second, many different drugs, not all of them SSRIs, were prescribed successively when others were deemed ineffective without any specification of a coherent rationale or timeline of trials being specified. Third, this study had only four participants. Finally, the institution that supported this research is Yaryura-Tobias' own psychological clinic in New

York.

It is difficult to determine whether fluoxetine was the cause of improvement in some cases in view of the fact that an array of co-therapies were applied in certain studies. In addition, even when the therapies were similar, conflicting results were found. Benjamin and Buot-Smith (1993) prescribed the opiod naltrexone along with fluoxetine, and it was concluded that only as a combination was the drug therapy advantageous. The same researchers simultaneously engaged in an unidentified behavioral program and rigid diet consisting of 900 kcal a day without commenting on what effect either of these had on the treatment. Yaryura-Tobias et al. (1998) also prescribed naltrexone for seven months in concurrence with fluoxetine and thioridazine, an antipsychotic, but found no improvement in skin picking while nonetheless reporting that cognitive and behavioral therapies added to the original drug therapy's success.

When reviewing treatment interventions of a single case study of an 11-year-old patient (Miss A), Martin et al. (1998) describe the drug regimen she was on during observation. This included the SSRI fluvoxamine, methylphenidate (a stimulant), valproate (an anticonvulsant and mood stabilizer), and lastly, growth hormone therapy. They state that improvement in "disruptive behaviors" was due to fluvoxamine, while valproate was meant to "target her mood lability" (Martin et al., 1998, p. 1268). It is not indicated how they came to the conclusion that fluvoxamine caused the reduction of the unwanted behaviors or what were the speculated effects of valproate. Because the two symptoms are similar in scope, it would be difficult to differentiate which drug affected them individually while Miss A was taking the medications simultaneously.

In addition to skin picking, fluoxetine appears to positively affect many behavioral problems that are associated with PWS. A decrease in oppositional behavior was reported (Benjamin & Buot-Smith, 1993; Warnock & Kestenbaum, 1992), as were lower incidences of violent

outbursts and hoarding (Hellings & Warnock, 1994). Food foraging was decreased (Warnock & Kestenbaum, 1992) and the addition of a "brighter mood" was observed in one patient (Martin et al., 1998, p. 1268). Another patient was observed to have better social exchanges overall (Benjamin & Buot-Smith, 1993). These findings could be of use in improving the lives of people with PWS and their caretakers if substantiated by further study.

Several negative side effects of SSRI use have also been reported in the literature. Severe headaches were seen in two case studies and were eliminated by lowering the dosage of fluoxetine administered (Warnock & Kestenbaum, 1992; Yaryura-Tobias et al., 1998). Martin et al. (1998) claim that people with PWS cannot always endure the standard dosage of medication given for their weight. This may mean that each individual patient needs to be carefully titrated onto an SSRI until reaching a safe and effective dose, or it may mean that people with PWS have a different universal standard that has not yet been found. What may be most problematic, though, is the claim that undesirable aggressive and compulsive behaviors seem to worsen in some cases at the beginning of treatment and when dosage is increased (Martin et al., 1998). These are important aspects of SSRI therapy that need to be taken into account when it is prescribed as well as in future research of the drugs.

Weight control is of great importance when considering treatment of the PWS population. The current literature is divided as to whether SSRIs have the side effect of weight loss and/or stability in people with PWS. Martin et al. (1998) found that they do not aid either aspect of weight control. However, Benjamin and Buot-Smith (1993) as well as Dech and Budow (1991) comment that the patients in their studies maintained and even lost a significant amount of weight only after treatment with fluoxetine began. Benjamin and Buot-Smith's (1993) findings are somewhat problematic, however, as the patient at six weeks of treatment was going to a gym on a regular basis for the first time in

her life, possibly due to the reported improvement in mood. There is no mention of this fact when proclaiming weight loss due to fluoxetine over a five and a half month period.

Results of studies of the efficacy of SSRI treatment of skin picking in persons with PWS are mixed. Instances in which treatment was abandoned and then reintroduced varied widely in outcome. In Benjamin and Buot-Smith's (1993) case the doctors ceased the use of the co-therapy naltrexone twice in order to test the benefit of fluoxetine alone on skin picking and food searching. Not only did fluoxetine fail to improve these symptoms, but also they seemed to worsen without naltrexone. The length of these trials may have been too short to fully support these findings, however. The first discontinuation of fluoxetine was only five days after its initiation, and the drug was reinstated 15 days later. The second termination of naltrexone occurred after a more reasonable 34 days, but it was restored just ten days later.

A different case in which unintentional interruption of fluoxetine intake took place had more positive findings with regard to SSRI success in treating skin picking. One of Hellings and Warnock's (1994) participants had to be taken off fluoxetine because he suffered from a bout of acute diarrhea. He had been taking the drug for over a year when this occurred, and he was seen to revert back to pretrial behaviors. Intensified skin picking along with hoarding and violent temper were described as "notable" (p. 247). There is no clarification of how the doctors came to this conclusion, and it appears to be based only on qualitative observation. Also, it is possible that the illness itself may have caused these symptoms to return rather than the discontinuation of fluoxetine.

Topiramate Research

Studies of topiramate with PWS patients are fewer in number, but more recent. Three studies were found that investigated topiramate's effect on skin picking in a total of 15 persons with PWS (Shapira et al., 2002; Shapira, Lessig, Lewis, Goodman, & Driscoll, 2004; Smathers et

al., 2003). All of them suggest that topiramate might be useful in treating this behavior. Different methods were engaged in making these assertions. They included: weekly physical check-ups by investigators (Shapira et al., 2002, 2004) and by staff at group homes in which the participants lived (Shapira et al., 2004), photographing lesions over time (Shapira et al., 2002), and questionnaires and phone surveys given to parents about their children's behavior (Smathers et al., 2003).

These three studies have particular limitations. Every study allowed participants to continue to take other prescription drugs while taking part in a topiramate trial, thus raising the possibility that topiramate is helpful as an additional treatment, but not necessarily on its own. Some of these accompanying drugs included fluoxetine and naltrexone, other potential treatments of skin picking in PWS. Also, Shapira et al.'s (2002, 2004) trial only lasted eight weeks, while Smathers et al. (2003) do not even specify what length of time they are reporting on, only that clinic visits were planned for up to "yearly thereafter" (p. 131).

There is no consensus in the literature about positive side effects of topiramate on behavior. Smathers et al. (2003) surmise that the drug had an overall effect of improved mood in all of their participants, while Shapira et al. (2002, 2004) did not look at mood.

Another favorable outcome during one trial was a reduction of compulsive behavior involving food and eating (Smathers et al., 2003). This data is subject to parental bias though as reporting of this behavior was obtained by questionnaires and phone calls. In contrast, Shapira et al. (2004) acquired different results using the standardized Yale-Brown Obsessive-Compulsive Scale checklist to review whether compulsive behaviors were reduced during their topiramate trial. They found no statistical significant reduction in compulsive behaviors. We may view this finding with caution, however, as the Yale-Brown Obsessive-Compulsive Scale is not a test for people with PWS specifically.

There were several adverse side effects also described in the literature. Both Smathers et al. (2003) and Shapira et al. (2002, 2004) noted increased sleepiness in patients taking topiramate. To combat this, the research teams administered the medication at bedtime. One person was seen to become more irritable in the beginning of the trial, but after eight weeks was restored to baseline level with no intervention (Shapira et al., 2002). Two female participants in the same study experienced word-finding difficulties. One of them also felt tingling in her foot. However, Shapira et al.'s (2004) paper concludes that side effects were minimal in scope and that topiramate was well endured in general.

The issue of topiramate's effect on weight control has been closely chronicled. Privitera (1997) found that topiramate differs from other anticonvulsants because of its side effect of weight loss. Shapira et al. (2002, 2004) cite this as part of the rationale for experimenting with it in patients with PWS. Two of the three participants in Shapira et al.'s (2002) study either did not gain weight or lost some, while the third gained four and a half pounds over the eight week trial. These varied results support the need for further research. A year later, Smathers et al. (2003) reported that all seven participants in their inquiry benefited in regards to weight while on topiramate; not a single case of weight gain took place. This contradicted Shapira et al.'s (2004) study of nine participants, which found no evidence of weight loss or increased weight stability when comparing BMI at baseline and eight weeks.

Later research suggests topiramate may have a weight loss mechanism, but that it is not triggered in people with PWS. In a study of 61 obese patients with binge-eating disorder (BED), there was a statistically significant loss of body mass over the 14-week trial as well as fewer weekly bingeing episodes (McElroy et al., 2004). The power of this study is heightened by the fact that it was randomized, double blind and placebo controlled, but it also had a high early termination rate as 26 participants dropped out.

Because BED has similar symptoms to PWS, such as obesity and compulsive eating, research in the use of topiramate in both disorders may shine light on how these symptoms are manifested in the biology of both of these groups.

In an attempt to pinpoint the origin of uncontrollable hunger in people with PWS in relation to topiramate, Shapira et al. (2005) used functional magnetic resonance imaging, better known as fMRI. They did one scan pre-treatment with topiramate and one post-treatment on three different adults with PWS who did not respond to the drug in regard to weight loss. When compared with other obese patients with no PWS, they found that the hypothalamus, where satiety is recognized, operates slower in those with PWS, with a difference of 11 minutes. When compared to normal weight people the disparity is even larger, at 14 minutes. This study may indicate an abnormality within the central nervous system that affects the ability of food intake to induce satiety in people with PWS. It could also lead to an abandonment of topiramate as a weight loss treatment for PWS patients, as no difference in satiety was found pre and post treatment in the hypothalamus. More research is indicated though, as a small sample was used and all participants were taking other medications at the time of the study.

Even if it does not help with weight control, topiramate's efficacy in treating skin picking behavior is well worth pursuing, as there is evidence of its success. Shapira et al.'s (2002) case report of three individuals states that each participant claimed that the desire to pick decreased while on the drug. All of them continued to take topiramate after the eight-week trial ended and maintained improvement of self-injurious behavior. These same participants performed better on the Gordon Diagnostic System's Delay Task while on topiramate. This ranks the ability to repress and postpone impetuous behavior, which is associated with skin picking. Also, in 2004, Shapira et al. tell of one participant's experience after ending eight months of topiramate treatment. After taking

lower amounts of the drug over time, a resurgence of skin picking behavior occurred. Other concrete observations that support the beneficial effects of topiramate are decreases in the count and measurement of lesions (Shapira et al., 2002, 2004). In the only study to utilize statistics, data were evaluated with the *t* test (Shapira et al., 2004). A significant reduction with treatment was found at the .01 level on the Self-Injury and Self-Restraint Checklist when comparing baseline and eight weeks of treatment.

Flaws in Research

All of the studies described here that directly addressed PWS use the method of open-label observation. It is possible that the effects of observer bias affected the experimenters and parents. These can include, but are not limited to, difficulty in obtaining objective observations and the skewing of results due to expectations. These studies are further restricted by the fact that observation can only describe the chosen behavior, but never account for the cause of it. Another variable that may have altered the results of these studies is the placebo effect. In other words, it is possible that the patients themselves altered their behaviors as a result of their own perception or anticipation of the results.

Research of SSRI and topiramate use in addressing self-injurious behavior in PWS has been limited to a small number of patients and done by a sparse number of researchers. This is probably because it is a rare disorder. A search of the literature revealed only twelve case studies on SSRI use in PWS. Two of them do not focus on skin picking, but instead on hair pulling, hoarding and violent temper (Dech & Budow, 1991; Hellings & Warnock, 1994). Interestingly, Warnock is listed as the author in two of the journal articles (Hellings & Warnock, 1994; Warnock & Kestenbaum, 1992) and two patients seem to be the same people in both articles. So, by that count, there may only be eight case studies that target SSRI use in treating skin picking in PWS. No judgment about the

treatment can be made based on such a low number of cases, as the samples may not be representative of the entire PWS population. Even though topiramate research includes a higher number of participants (15), it is also impossible to consider this a representative sample. This number counts the three participants in both Shapira et al.'s 2002 and 2004 studies only once.

Allowing participants to remain on concomitant drug therapies is detrimental to findings, as there is no way to ensure that the trial drug alone was effective. Most of the studies discussed involved patients who were taking more medications than the drug on trial.

There was no universal standard for measuring either sores or the behavior of skin picking itself, although Shapira et al. (2002) photographed patients in their case studies of three patients. Even then, they did not begin the documentation in one case until after topiramate use had begun. Smathers et al. (2003) relied on parental reporting which in itself is problematic, as expectations as well as desired change of behavior may have affected the data. While weekly check-ups by doctors and researchers is important, only one case was said to look at the patient fully naked as she had been noted to hide the behavior (Shapira et al., 2002). It is difficult to substantiate the results of these studies without the means of definitive measurements of skin picking and lesion size.

Conclusion

Although both SSRIs and topiramate appear to be promising treatments for skin picking in PWS, it is impossible to ascertain whether they are effective drug therapies at this time. There is not enough published evidence devoid of methodological problems to comprehensively support the efficacy of either one. However, all studies reviewed for this investigation do indicate that more research is needed as both SSRIs and topiramate demonstrated that in some instances they seem to alleviate skin picking behavior.

Suggestions for Further Research

Wigren and Heimann's (2001) survey found that 70% of participants that actively engaged in skin picking behavior did so when alone. Sixty-one percent of those parents informed the researchers that they believed their children not only performed the behavior secretly but also attempted to conceal any resultant injury. These findings emphasize a need for orderly methods in documenting how often participants skin pick so that the rate of the behavior can be accurately measured. This could be done by observing participants behind a two-way mirror for a certain amount of time per day while tallying how often they exhibit skin picking behavior over the course of the study. Also, photographing existing sores at baseline and any newly developed sores during treatment would ensure proper verification of results. In order to thwart issues of concealed lesions, periodic full body exams could be part of the methodology. The possibility of reinforcing the behavior of skin picking with these exams (Hellings & Warnock, 1994) would have to be taken into consideration and controlled.

The largest total number of participants in any of the studies concerning drug therapy and skin picking mentioned was eight (Shapira et al., 2004). Clearly, more participants are needed to validate the accuracy of population representation. This could prove difficult, as PWS itself is a rare disorder. A further complication may be that recruiting children and mentally retarded adults with PWS would require obtaining informed consent from guardians.

Some of these studies recruited people through group homes that specialized in PWS care (Shapira et al., 2002, 2004), through referral or in-patient hospital care (Benjamin & Buot-Smith, 1993; Dech & Budow, 1991; Hellings & Warnock, 1994; Warnock & Kestenbaum, 1992; Yaryura-Tobias et al., 1998) or through the use of PWS non-profit group lists (Stein et al., 1994; Wigren & Heimann, 2001). It may prove difficult to recruit participants without these methods, but to avoid sample bias a more random procedure

must be used in enrolling and assigning them.

Future research of SSRI and topiramate treatment of skin picking would benefit by arranging trials of appropriate time lines. Shapira et al.'s (2002, 2004) research only tested topiramate for an eight-week period. Longer trials would help authenticate findings. Of course, a review of known data concerning the safety of a particular drug would have to be taken into consideration when planning the duration of experiments.

Regardless of specific experimental design, studies that investigate the efficacy of these drugs should be double-blind and placebo-controlled. This would safeguard against the bias associated with researchers and participants. It may also be useful to directly compare SSRIs and topiramate in one study. Ethical issues may arise regarding the use of placebo in a population that is characterized as being mild to moderately mentally retarded, however. Guidelines for this type of situation would have to be reviewed by researchers and the Institutional Review Board in charge of approving the research.

A further control needed to increase the potency of subsequent investigation of SSRI's and topiramate is testing them as monotherapies. It would be ideal if none of the participants were taking other prescription drugs. Also, if any behavioral therapies were to be used, they would need to be used on all participants uniformly.

In order to clearly assess behavioral problems other than skin picking, standardized tests may be of use. Shapira et al. (2004) had much success with this in recording compulsivity. Care should be taken when deciding which to use with regard to the attributes of PWS, such as IQ of participants. It may even be advantageous to formulate new tests designed solely to measure particular behaviors in people with PWS.

Finally, empirical research must eventually be based on more than individual case reviews, and must ultimately rely on statistically significant findings. If a large enough sample can be found and valid, reliable data collected, the appropriate statistical test can be found depending on the design of the experiment.

PWS presents symptoms that adversely affect patients and their families. These preliminary findings that SSRIs and topiramate may alleviate skin picking and other self-injurious behaviors necessitates that these drugs be more extensively tested in larger, better-controlled studies.

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